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Gram-Negative Bacterial Endocarditis in Narcotic Addicts

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The number of cases of bacterial endocarditis in drug addicts seen at UCLA and Wadsworth Veterans Administration hospitals increased sharply in 1971 over the average of the four preceding years. Enteric Gram-negative bacilli were the infecting organism in three of the seven cases seen in 1971 but were not found in any cases of endocarditis in the 1967-70 period.

Medical treatment of the patients was, in general, unsuccessful in spite of the intensive use of newer antimicrobials active against enteric Gram-negative bacilli. One patient died with fulminant Pseudomonas endocarditis and two others (Pseudomonas and Serratia endocarditis) eventually required operations on the heart before a cure was achieved.

INTRAVENOUS INJECTION OF ILLICIT NARCOTICS has become increasingly prevalent in the United States. Drug addicts are likely to have a variety of medical complications, including bacterial endocarditis.[1] Published reports indicate that the Gram-positive cocci remain the most frequently isolated organisms from cases of endocarditis in addicts.[2,3] However, recent experience in our hospitals suggests that more and more of these cases are caused by enteric Gram-negative bacilli. These organisms are frequently resistant to multiple antibiotics, making medical therapy extremely difficult. This report consists of three case histories of enteric Gram-negative endocarditis in addicts and data comparing the incidence of bacterial endocarditis in the twelve-month period of 1971 with that of the previous four years, 1967 to 1970.

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Clinical Data

All patients were hospitalized either at the UCLA Hospital, a 600-bed university referral center, or the Wadsworth Veterans Administration (WVA), Hospital, a 900-bed general medical and surgical hospital. The patients all had positive blood cultures and signs and symptoms of bac-

terial endocarditis, including evidence of valvular heart disease. We include in our definition of enteric Gram-negative bacilli members of the family Enterobacteriaceae and the genus Pseudomonas.

Summaries of Cases

CASE 1. A 41-year-old man, a heroin addict who had been successfully treated for enterococcal (Streptococcus faecalis) endocarditis of the mitral valve in December, 1968, was admitted to WVA Hospital August 20, 1971, with fever and congestive heart failure. Multiple blood cultures taken at the time of admission grew Pseudomonas aeruginosa. A clinical diagnosis of bacterial endocarditis was made and the patient was initially treated with intramuscular gentamicin in a daily dose of 6 mg per kg of body weight. Intravenous carbenicillin was added at a dose of 36 grams per day with 1 gram of probenecid. He became afebrile and improved clinically. The minimum inhibitory concentrations (MIC) of gentamicin and carbenicillin for the patient's Ps. aeruginosa were 6.25 mcg per ml and 200 mcg per ml respectively. Measured serum levels of these antibiotics were 5.0-7.5 mcg per ml and 100 to 200 mcg per ml respectively. This isolate of Ps. aeruginosa was able to grow in undiluted serum from the patient obtained during therapy. After six weeks of treatment, blood cultures again grew Ps. aeruginosa. The MIC to gentamicin was now 12.5 mcg per ml. In addition, symptoms of mild eighth nerve toxicity appeared. Gentamicin and carbenicillin were discontinued and combined therapy with sulfadiazine, trimethoprim, and polymyxin B was instituted in daily doses of 6.0 grams orally, 960 mg orally and 135 mg intramuscularly, respectively. *In vitro* susceptibility testing had suggested that this combination might be therapeutically effective. The addition of sulfadiazine and trimethoprim appeared to enhance the bactericidal activity of polymyxin B (MIC reduced from 0.75 mcg per ml to 0.2 mcg per ml). The patient was afebrile and asymptomatic for 19 days while receiving this therapy. However, a slight fever then developed and Ps. aeruginosa was recovered from three blood cultures. The triple combination of antimicrobials was therefore stopped and a third treatment program was begun, this time using a combination of tobramycin (nebramycin) and carbenicillin in daily doses of 300 mg intramuscularly and 36 grams intravenously, respectively. The MIC to tobramycin was 6.25 mcg per ml and serum levels of 2.75 to 6.2 mcg per ml were measured. The patient once again became afebrile but showed little clinical improvement otherwise. Therefore, after a further month of medical treatment, cardiac operation was performed with debridement of a vegetation from the mitral valve. Two weeks after operation the patient was discharged from the hospital on no antimicrobial therapy.

CASE 2. A 41-year-old man who was addicted to heroin was successfully treated for tricuspid endocarditis due to Staphylococcus aureus in December, 1970. Subsequently he resumed intravenous heroin use and in April, 1971, chills and fever developed with jaundice and ankle edema. He was admitted to a hospital and a diagnosis of tricuspid valve endocarditis due to Serratia marcescens was made. This original isolate was susceptible to chloramphenicol and gentamicin (MIC for both agents 1.5 mcg per ml). Despite eight weeks of therapy with gentamicin (5.0 mg per kg per day), fever and positive blood cultures persisted. A Serratia isolate obtained at this time was resistant to gentamicin (MIC >25 mcg per ml) and treatment with chloramphenicol intravenously (4.0 grams per day) was begun. A month of this therapy followed by a week of combined gentamicin-chloramphenicol therapy was unsuccessful. A third Serratia isolate was now resistant to all antibiotics in common usage (MIC's to chloramphenicol and gentamicin both >25 mcg per ml). The patient was transferred to the WVA Hospital August 6, 1971, with chills and fever and the murmur of tricuspid valve insufficiency. *In vitro* studies showed that the combination of sulfadiazine, trimethoprim, and polymyxin B was bactericidal for the third Serratia isolate at concentrations within the therapeutic range. Treatment was begun with a combination of sulfadiazine 6.0 grams per day by mouth, trimethoprim 1.0 gram per day by mouth and polymyxin B 120 mgs per day intramuscularly. The patient became afebrile and blood cultures were sterile. This therapy was stopped after eight weeks, and two weeks later a relapse of the infection occurred. The three-drug combination was resumed and again the patient became afebrile and blood cultures were sterile. His general condition progressively improved over the next ten weeks until, rather abruptly, azotemia, hematuria (without crystalluria), eosinophilia, and fever developed. The antimicrobial agents were stopped because of suspected toxicity and blood cultures taken one day later, again grew Serratia marcescens. Gentamicin and chloramphenicol were temporarily re-

instituted and one week later cardiac operation was performed for removal of the tricuspid valve. Cultures of the valve yielded Serratia marcescens. Postoperatively, fever disappeared and blood cultures were sterile.

CASE 3. A 39-year-old woman, a heroin addict, was admitted to the UCLA Hospital August 2, 1971, with a five-day history of chills, fever and painful spots on the arms and legs. Florid lesions of bacterial endocarditis were present, including splinter hemorrhages and Roth spots. There was a loud cardiac murmur of mitral insufficiency, and the spleen was enlarged. The temperature was 40°C (104°F). Microscopic hematuria was present and the cerebrospinal fluid showed pronounced pleocytosis. Nine of ten blood cultures grew Pseudomonas aeruginosa. The patient was treated with a combination of gentamicin and carbenicillin in doses of 4.5 mg per kg per day intramuscularly and 24 gm per day intravenously, respectively. *In vitro* tests with the Pseudomonas isolate demonstrated an MIC of 1.56 mcg per ml for gentamicin and 200 mcg per ml for carbenicillin. Measured peak serum levels for gentamicin were 3.8 to 5.7 mcg per ml and for carbenicillin were 400 to 800 mcg per ml. A 1:16 dilution of the patient's serum obtained during therapy killed a Pseudomonas isolate. Her condition improved slightly at first but then rapidly deteriorated as meningitis, endophthalmitis, and hepatic failure developed. Intrathecal and subconjunctival injection of gentamicin were futile and the patient died on the thirteenth hospital day. A postmortem examination revealed vegetations on the mitral valve.

None of 57 cases of bacterial endocarditis seen at UCLA and Wadsworth hospitals between 1967 and 1970 was caused by enteric Gram-negative bacilli (Table 1). There were three cases of endocarditis in narcotic addicts during this period and all were caused by Gram-positive cocci. One of these cases occurred in 1968 and the other two were in 1970. In contrast, during 1971, there were four cases of endocarditis due to enteric Gram-negative bacilli, three of which were found in narcotic addicts. The fourth was in a patient with a prosthetic heart valve.

Between 1967 and 1970, 57 cases of endocarditis were seen, an average of 14.3 per year. Three of these (5.3 percent) occurred in addicts. In 1971, a total of 29 cases of endocarditis were seen, seven (24 percent) in addicts.

TABLE 1.—*Data on Cases of Bacterial Endocarditis at the UCLA-WVA Hospitals During the Four Years 1967-70 and from January 1, 1971 to December 31, 1971*

	1967-70	*1971*
Total number of cases	57	29
Cases in non-addicts due to enteric Gram-negative bacilli	0	1
Cases in addicts due to enteric Gram-negative bacilli	0	3
Cases in addicts due to Gram-positive cocci	3	4
Total number of cases in addicts	3	7

Discussion

Cherubin and Neu[4] observed an increase in the association of narcotic addiction with endocarditis, from 0.4 percent in 1948-57 to 3.9 percent in 1958-67. An average of 5.3 percent of the cases of bacterial endocarditis seen at UCLA-WVA hospitals from 1967-70 occurred in addicts. In 1971 it was 24 percent. These data suggest that narcotic addiction as a cause of endocarditis is increasing in importance and that this increase has occurred quite recently. In fact, of the ten cases of endocarditis in addicts treated in our hospitals since 1967, nine were seen in 1970 and 1971. Moreover, this increase has contributed significantly to a 100 per cent increase in the incidence of all cases of bacterial endocarditis at UCLA-WVA hospitals.

Previous reports emphasize the importance of Gram-positive cocci in addict endocarditis. Ramsey et al[3] noted only seven of 93 cases (7.5 percent) due to enteric Gram-negative bacilli. Cherubin et al[2] and Louria et al[5] reported an incidence of 13.5 percent and 15 percent, respectively. Our data from 1967 to 1970 reveals no cases of Gram-negative endocarditis. However, in 1971 three of seven cases (43 percent) were caused by these organisms. This experience at UCLA-WVA hospitals suggests that enteric Gram-negative bacilli are of increasing importance in the etiology of addict endocarditis.

There are probably multiple reasons for an increase in Gram-negative endocarditis in addicts. Two of our three patients had had previous episodes of Gram-positive endocarditis. They required extensive stay in hospital and were treated with prolonged courses of antibiotics that were inactive against Gram-negative bacilli. Moreover, many addicts spend considerable time in hospital for treatment of other complications of addiction. This experience indicates ample opportunity for

colonization with antibiotic-resistant enteric Gram-negative bacilli. These organisms, including Pseudomonas and Serratia, are recognized as frequent contaminants of the hospital environment and as the causes of many nosocomial infections.[6] Once colonization has occurred, repeated non-sterile intravenous injections offer a ready pathway into the addict's bloodstream.

Our third patient (who had Pseudomonas endocarditis) had not been ill or in hospital previously. However, since addicts commonly share their intravenous equipment,[7] Pseudomonas may have been acquired from another "hospital-colonized" addict. Moreover, the frequent practice of diluting the narcotic with ordinary tap water, toilet bowl water, or commercial "purified" drinking water is another possible source. Pseudomonas, in particular, is able to survive in moist environments such as sink traps and faucet filters.[8,9]

The failure of intensive treatment of our three patients with various antimicrobial agents serves to reinforce the impression that Gram-negative endocarditis seldom is cured by medical therapy alone.[3,10,11] Cures have been recorded in cases where simple debridement of vegetations or valvulectomy (with or without prosthetic valve replacement) have been combined with antimicrobial therapy.[12,13] In Case 1 herein reported, Pseudomonas endocarditis was cured only after debridement of the mitral valve and in Case 2 the patient (who had Serratia endocarditis) eventually required resection of the tricuspid valve.

Although medical therapy was not totally effective in our patients, suppression of bacteremia was achieved, enabling them to improve so that chances for surviving cardiac operation were greatly enhanced. The combination of gentamicin and carbenicillin was used in Case 1 because of the frequent synergistic activity of these agents against Pseudomonas.[14,15] However, this therapy alone was not curative, and in Case 3 also it was ineffective in controlling fulminant endocarditis. Tobramycin, a new aminoglycoside antibiotic reported to have enhanced activity against Pseudomonas,[16] was also used in Case 1. Although the MIC to tobramycin was relatively high, this agent, in combination with carbenicillin, appeared to control the bacteremia.

The Serratia marcescens recovered from the patient in Case 2 sequentially developed resistance to gentamicin and chloramphenicol, the only antimicrobial agents to which it was originally susceptible. This led to the use of the combination of polymyxin B, sulfadiazine and trimethoprim. The latter two agents act synergistically and have been used together in a variety of infections.[17,18] It has been suggested that combining either a sulfonamide or trimethoprim or both with a polymyxin results in additional synergistic activity against a number of Gram-negative bacilli.[19-22] During therapy with such a triple combination, the patient in Case 2 was abacteremic and clinically improved. However, it is clear from the early relapse after discontinuation of treatment that this regimen had not cured the Serratia endocarditis. Moreover the triple combination, when used in Case 1, suppressed the bacteremia for only 19 days. Although these newer antimicrobial agents have been of some benefit, our experience suggests that they are not curative in Gram-negative bacterial endocarditis.

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